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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: TREATMENT OF NEUROTIC DISORDERS

(57) Abstract: Use of the escitalopram (the S-(+)-enantiomer of citalopram) or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of neurotic disorders is provided, including anxiety states, in particular generalised anxiety disorder and social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder and panic attacks.

animal models for anxiolytic effect and effect on panic attacks and for obsessive compulsive disorder, respectively.

According to the invention, escitalopram or a pharmaceutically acceptable salt thereof may be administered in any suitable way e.g. orally or parenterally, and it may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the compound of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule or in the form of a suspension, solution or dispersion for injection.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tabletting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, flavourings, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

The compound of the invention is most conveniently administered orally in unit dosage forms such as tablets or capsules, containing the active ingredient in a dose from about 1.0 mg to 50 mg, preferably 5 mg/day to 40 mg/day, most preferably 10 mg/day to 20 mg/day.

The oxalate of escitalopram may be prepared as described in US Patent No 4,943,590 and the base and other pharmaceutically acceptable salts may be obtained therefrom by standard procedures.

Thus the acid addition salts used according to the invention may be obtained by treatment of escitalopram with the acid in an inert solvent followed by precipitation, isolation and optionally re-crystallisation by known methods and if desired micronisation of the crystalline product by wet or dry milling or another convenient process, or preparation of particles from a solvent-emulsification process.

Pharmacological Tests

Escitalopram was tested in well recognised and reliable test models of effects on neurotic disorders. Citalopram-racemate was included for comparison purposes.

The footshock- induced vocalisation test in adult rats.

The footshock- induced vocalisation test in adult rats (described in detail in Sánchez C., Effect of serotonergic drugs on footshock-induced ultrasonic vocalization in adult male rats. *Behav. Pharmacol.* **1993**; *4*:267-277) is a test for anxiolytic and anti-panic effects.

Experimental Procedure

Male rats (Wistar WU, Charles River, Germany), weighing 150-175 g at the beginning of the study were used.

Briefly, test cages (22 cm x 22 cm x 22 cm) made of grey Perspex and equipped with a metal grid floor were used. Footshocks were delivered from a two pole shocker and a microphone sensitive to ultrasounds in the range of 20-30 kHz was placed in the centre of the lid of the test cage. The ultrasounds were sent from the microphone to a preamplifier and converted from AC signals to DC signals in a signal rectifier. The accumulated time, in which the voltage of the rectified signal was larger than the voltage of a previously determined treshold level, was recorded.

Twenty-four hours before the first test session the animals were primed. A rat was placed in each test cage and received, immediately thereafter, four 1.0 mA inescapable footshocks each of a duration of 10 sec and with an intershock interval of 5 sec. The animals were left in the test cage for 6 min after the last shock. On test days, drug or saline was given 30 min before test. The rats received four 1.0 mA inescapable footshocks each of a duration of 10 sec. The intershock interval was 5 sec. Recording of ultrasonic vocalisation started 1 min after the last shock and lasted for 5 min. The total time spent on vocalisation was recorded. After a wash-out period of one week the rats were used in a new test session. The rats were used for a total of 7-8 weeks. At each test session, the animal groups were randomly allocated to treatment with saline or test drug. Each treatment group consisted of 8 animals,

one saline and 2-4 drug treated groups were included at each session. Each drug was tested at least in two separate experiments with overlapping doses.

Results

The experiments showed that the maximum effect was 60-70% inhibition for citalopram-racemate whereas escitalopram was able to inhibit vocalisation completely.

Black and White Box Test

This is a test for anxiolytic effects. The test model is further described in Sánchez, C. (1995) Pharmacol. Toxicol. 77, 71-78.

Test procedure

Male mice (Lundbeck strain, Charles River, Germany) weighing 30-35 g were housed in groups of 4 in macrolon cages type II under a reversed 12 h day /night cycle (lights off 7 p.m.). The mice were adapted to the reversed light/dark cycle for at least 3 weeks prior to testing. The room temperature (21 ± 2°C), relative humidity (55 ± 5%), and air exchange (16 times per h) were automatically controlled. The animals had free access to commercial food pellets and water.

The test box used was designed as described by Sánchez (1995) (*supra*). Briefly, the test box (45 cm x 27 cm x 27 cm) was open-topped and divided into two compartments (ratio 2:3) by a partition which was black on the side facing the black compartment and white on the side facing the white compartment. The smaller chamber was made of black perspex. The larger chamber was made of white perspex except for the lowest 7.5 cm. This part was made of transparent perspex (outer walls) and black perspex (partition). The white compartment was connected to the black compartment by a 7.5 cm x 7.5 cm opening in the partition. The floor of the white compartment was divided into 9 fields, and the floor of the black was divided into 6 fields. The white compartment was illuminated by means of a Schott KL 1500 electronic lamp emitting cold light corresponding to a light intensity of 560 Lux. The mouse test-system was fully automated by 2 rows of 11 infrared light sources and photocells in the transverse direction and 1 row of 16 in the longitudinal direction (lower row). The lower row of photocells (2 cm above cage floor) detected horizontal locomotor activity (crossing, entries, and time in each compartment), whereas the upper row of photocells (5 cm above

cage floor) detected rearing activity. The accumulated data for 1 min intervals were recorded from 4 test boxed simultaneously and stored in a Paradox data base.

The test boxes were placed in a dark and quiet room. The mice were transported to the test room in a darkened container about 2 h before test. The test room was separated into two parts by a black curtain. The drug treatment took place in one part of the room using a minimum of red light. After dosing, the mice were placed individually in macrolon type II cages until test. The pretreatment time was 30 min. The test boxes were placed in the other part of the room. The test was started by placing the mouse in the centre of the brightly-lit white compartment facing the opening to the black compartment. The test duration was 5 min and the number of rears and line crossings between squares in both the black and the white compartment, number of entries into the black compartment and time spent in the white compartment were assessed.

Results

Escitalopram showed prominent effects in this model.

Schedule-induced Polydipsia

Food deprived rats exposed to a procedure in which food is delivered intermittently will drink large amounts of water if given the opportunity to do so. This behavioural phenomenon is called schedule-induced polydipsia and can be considered as an excessive expression of a normal behaviour. Schedule-induced polydipsia is regarded as a model of obsessive-compulsive disorder (Woods et al. 1993).

Test Procedure:

Male wistar rats (Møllegård) housed in pairs and kept on a food-restricted diet (80% of normal body weight) for 2 weeks before the start of testing and throughout the duration of testing. To induce polydipsia rats were placed in test chambers where a pellet dispenser automatically dispensed one 60 mg food pellet every 60 seconds. Water was available at all times in the test chamber. Rats were tested 4-5 times per week, after 3-4 weeks training 70% of the rats were drinking >10ml per 30 min test session.

Once the rats had attained a steady drinking level compounds could be tested. Citalopram (40 mg/kg) or Lu 26-054 (20 mg/kg) were administered orally 60 min prior to testing and at

10:00 on the non-test days. The water intake was presented as a percentage of the pre-dosing (baseline) level.

Results:

Escitalopram produced a significant reduction in water intake, whereas citalopram was without effect.

All these studies show that escitalopram has potent anti neurotic diseases effects, in particular anxiolytic effects and effects on panic attacks and obsessive compulsive disorder.

Claims

1. Use of escitalopram or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment of neurotic disorders.

2. The use according to Claim **1, characterised in,** that the medicament is for administration as a unit dose.

3. The use according to Claim 1 or **2, characterised in,** that the unit dose is containing the active ingredient in an amount from 1.0 mg to 50 mg, preferably 5 mg/day to 40 mg/day, most preferably 10 mg/day to 20 mg/day.

4. Use of any of Claims **1** to **3, characterised in,** that the medicament is for the treatment of generalised anxiety disorder.

5. Use of any of Claims **1** to **3, characterised in,** that the medicament is for the treatment of social anxiety disorder.

6. Use of any of Claims **1** to **3, characterised in,** that the medicament is for the treatment of post traumatic stress disorder.

7. Use of any of Claims **1** to **3, characterised in,** that the medicament is for the treatment of obsessive compulsive disorder.

8. Use of any of Claims **1** to **3, characterised in,** that the medicament is for the treatment of panic attacks.

9. Use of any of Claim **8, characterised in,** that the medicament is for the treatment of panic disorder.

10. Use of any of Claim 8, **characterised in**, that the medicament is for the treatment of specific phobias.

11. Use of any of Claim 8, **characterised in**, that the medicament is for the treatment of social phobia.

12. Use of any of Claim 8, **characterised in**, that the medicament is for the treatment of agoraphobia.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00377

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/343, A61P 25/00, A61P 25/22
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, MEDLINE, CAPLUS, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Rev. Contemp. Pharmacother, Volume 10, 1999, A. F. Joubert et al., "Citalopram and Anxiety Disorders" page 79 - page 131 --	1-12
X	ACTA PSYCHIATRICA SCANDINAVICA, Volume 96, 1997, Koponen H. et al., "Citalopram an the treatment of obsessive-compulsive disorder: an open pilot study" page 343 - page 346 --	1-3,7
X	Journal of Serotonin Research, Volume 1, 1996, Dan J. Stein MB et al., "Use of serotonin selective reuptake inhibitor citalopram in obsessive-compulsive disorder" page 29 - page 33 --	1-3,7

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	J Clin Psychiatry, Volume 59, No 10, October 1998, Ulla M. Lepola et al., "A Controlled, Prospedtive, 1-Year Trial of Citalopram in the Treatment of Panic Disorder" page 528 - page 534	1-3,8-12
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INTERNATIONAL SEARCH REPORT

Information on patent family members

03/10/00

International application No.
PCT/DK 00/00377

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Information on patent family members

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International application No.
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